1. Applicants note the confirmation of the election of Group IV, claims 35-40 and 42-48. However, Applicants submit that this election was made with traverse, and that supposed errors were pointed out in Paper No. 19. Acknowledgement is respectfully requested.

Applicants have corrected spelling errors in the application as pointed out by the Examiner.

The Office Action notes sequences in the specification that require inclusion in the Sequence Listing. Applicant respectfully points out that the sequences on pages 30-32 of the specification are marked in the specification as SEQ ID Nos. 21 and 22, and are properly included in the Sequence Listing previously submitted. Applicants have included the sequences on pages 42, 54, and 63 in the amended Sequence Listing filed herewith.

I hereby state that the content of the Sequence Listing and the computer-readable copies of the Sequence Listing submitted in accordance with 37 C.F.R. § 1.821(c) and (e), respectively, are the same. I further state that this submission, filed in accordance with 37 C.F.R. § 1.821(g), does not include new matter.

2. Claims 35-40, 42-46, 49-54, 62-70, and 72-74 are rejected under 35 U.S.C. § 101 because the claimed invention allegedly lacks patentable utility. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants submit herewith as Exhibit A a copy of Bitgood et al., *Current Biology* **1996**, *6*, 298-304, published prior to the filing of the present application. This abstract indicates that mouse Desert hedgehog regulates testicular function, particularly spermatogenesis in mice. Applicants also submit herewith as Exhibit B a portion of a BLAST search, which indicates on page 4 that mouse Desert hedgehog is 96% identical to human Desert hedgehog, the query sequence of this report. Applicants thus submit that, as of the time of filing of the present application, one of skill in the art would have expected human Desert hedgehog to have a similar utility in humans, because the hedgehog signalling pathway was known to be highly conserved, performing similar functions in organisms as dissimilar as fruit flies, mice, and humans. This understanding is underscored by Chang et al., *Development* **1994**, *120*, 3339-3353, submitted herewith as Exhibit C, which indicates that Hhg-1, a mouse Sonic hedgehog gene, functions in

Drosophila in a manner similar to the native *Drosophila* hedgehog protein, as described on pages 3344-3347, despite the fact that these polypeptides are only approximately 46% identical. Chang et al. note, however, that the amino-terminal portion of these two proteins are 69% identical, page 3343, left column, and that the Hhg-1 product undergoes proteolytic cleavage, as indicated on pages 3348-3349 and Figure 9.

Furthermore, Applicants respectfully point out that PCT WO95/18856 to Ingham et al., a copy of which is furnished herewith as Exhibit D, indicates on page 13, lines 20-22, that Sonic hedgehog undergoes proteolytic cleavage at two sites to form a 19 kD fragment and a 27 kD fragment. From page 79, line 27, to page 81, line 5, the similarity of the various proteins in the hedgehog family is taught. From page 79, line 34, to page 80, line 2, the application contemplates that mouse Dhh is cleaved between positions 22 and 23, as depicted in Figure 5, and the high similarity between mouse and human sequences strongly suggests a similar cleavage in humans. Porter et al., *Science* **1996**, *274*, 255-259, included herewith as Exhibit E, indicates that the N-terminal cleavage product is responsible for the bioactivity of hedgehog proteins, as presented in the abstract and throughout. In light of the long-recognized high degree of similarity in the N-terminal portions of hedgehog polypeptides, particularly between mouse and human Desert hedgehog in this region, and the understanding that this region is primarily responsible for the biological activity, one of skill in the art at the time of filing would have expected human Dhh to exhibit biological activity similar to the known homologs. Moreover, the fact that Hhg-1, despite being only 69% identical to *Drosophila* Hh in the N-terminal portion, can perform the functions of *Drosophila* Hh in *Drosophila* would lead one of skill in the art to expect that human Desert hedgehog, which also exhibits strong homology to the N-terminal regions of Hhg-1 and *Drosophila* Hh as can be seen on pages 7 and 21 of Exhibit B, would show activity in *Drosophila*, mice, and humans.

Applicants respectfully direct the Examiner's attention to MPEP 2107.01, which discusses the procedural requirements for a rejection on the basis of lack of utility. As entry III.A. indicates, an asserted utility, as is the case in the present application, creates a presumption of utility. "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement... unless there is a reason for one skilled in the art to

question the objective truth of the statement of utility or its scope." (emphasis in original) *In re Langer*, 183 USPQ 288 at 297 (CCPA 1974). As indicated in entry III.B., an assertion is credible "unless (A) the logic underlying the assumption is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." In contrast, the Office Action simply alleges that the "specification does not teach the binding of human Desert ... hedgehog to patched protein or the resulting effect from such binding. The specification does not teach the homology between human Desert ...hedgehog proteins and any other proteins for which the function is known. Therefore, it is not clear that the nucleic acids encoding the proteins have a disclosed use." These statements of unsupported conclusion fail to point out errors in the logic of Applicants' asserted utility, and thus cannot meet the requisite legal burden for establishing a *prima facie* case of lack of utility.

The Examiner's attention is further directed to MPEP 2107.02, which discusses considerations relevant to therapeutic and/or pharmacological utilities. Applicants submit that the presently claimed invention clearly satisfies the tests indicated in entries I and II of this section, because the claimed invention bears a "reasonable correlation between the activity in question and the asserted utility" and shows "evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility". Furthermore, Applicants have pointed to literature references, published prior to the filing of this application, which support both of these positions. Accordingly, Applicants submit that one of skill in the art at the time of filing would have recognized human Desert hedgehog as having credible, substantial utility, and respectfully request reconsideration and withdrawal of this rejection.

3. Claims 35-40, 42-46, 49-54, 62-70, and 72-74 are rejected under 35 U.S.C. § 112, first paragraph, in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

With respect to claims 35-43, these claims were originally presented and thus do not raise an issue with respect to written description. The mere fact that the Examiner doubts that the proteins having a sequence of SEQ ID No. 17 or fragments thereof have the function set forth in

these claims has no relevance to the written description requirement. The Examiner's attention is directed to MPEP 2163, which discusses the written description requirement. Section 2163.01 points out that the test or analysis of the written description requirement is the same, and section 2163.03 states that the written description requirement "issue can arise in a number of different circumstances where it must be determined whether the subject matter of a *new* or *amended* claim is supported in an application as filed." (emphasis added) As these claims were neither new nor amended prior to this Response, Applicants assert that the written description rejection as applied to these claims is erroneous and should be withdrawn, a position fully supported by *In re Koller*, 204 USPQ 702 (CCPA 1980), which notes that original claims constitute their own description.

With respect to the claims added by preliminary amendment, as the Examiner appears to be questioning only the written description for the function of the claimed sequences. As this feature was presented in the originally filed claims, Applicants submit that adequate written description exists with respect to these claims as well. If the Examiner wishes to maintain this rejection, Applicants respectfully request that the grounds for the rejection be explicitly and precisely stated.

4. Claims 35-40, 42-46, 49-54, 62-70, and 72-74 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action alleges that "the state of the art at the time of filing was such that little was known about hedgehog proteins other than Shh." However, Applicants have cited a number of references above which question the factual basis for this assertion, and provide a strong indication that human Dhh would function in mice, if not in humans, as mouse Dhh functions in mice. Although, as noted by the Office Action, the present application does not explicitly set forth the homology between human Ihh and Dhh and other hedgehog proteins, one of ordinary skill in the art could readily perform such comparisons, as shown in the PCT application to Ingham et al., Exhibit D, and as exemplified by Exhibit B. Moreover, the obviously high level of

similarity between human Dhh and mouse Dhh, in addition to the widely recognized high level of similarity between the biologically active N-terminal portions of a wide range of hedgehog proteins, as noted above, would be ample evidence to one of skill in the art at the time of filing that the proteins encoded by the claimed nucleic acids would have the specified functions. In addition, it was also generally understood that hedgehog proteins in general acted by binding to patched, as described by Bitgood et al., from page 302-303, and by Ingham et al. on page 47, lines 22-26. Patched, too, is highly conserved among diverse species, lending further credence to Applicants' assertions as set forth in the application as filed.

In light of these teachings which pervade the prior art, Applicants direct the Examiner's attention to MPEP 2164.04. This section delineates the Examiner's burden "to establish a reasonable basis to question the enablement provided for the claimed invention." Specifically, "it is incumbent upon the Patent Office, whenever a rejection on this basis, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

Applicants submit that the Office Action fails to meet this burden. Rather than providing the requisite evidence or reasoning, the Office Action simply asserts that enablement is lacking. Statements such as "it is not clear that the function of human Ihh or Dhh is the same as mouse Ihh or Dhh or as human Shh" or that "the specification does not teach the binding of human Desert or Indian hedgehog to patched protein or the resulting effect from such binding" are not based on the requisite level of sound reasoning or evidence, and are merely conclusory assertions insufficient to create a *prima facie* case of non-enablement.

Furthermore, even had the Examiner provided supported the above assertions, Applicants submit that the knowledge in the art at the time of filing, as exemplified by the various Exhibits submitted herewith, is more than sufficient to demonstrate the undue experimentation would not be required to practice the claimed invention. The Examiner is respectfully reminded that the test of enablement, as set forth in MPEP 2164.01, "is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Applicants submit that one of skill in the art could

readily use the technique of combinatorial mutagenesis to prepare a large number of polypeptides encoded by nucleic acids as set forth in the present claims, and test them for interaction with *patched*, using assays well known in the art and described in the present application.

Additionally, with respect to claim 35, Applicants submit that Bitgood et al, Exhibit A, supports the enablement of the claim term relating to regulation of testicular germ line cells. As described above, mouse Desert hedgehog had shown activity in Sertoli cells prior to the filing of the present application (see Bitgood et al.), and human and mouse Desert hedgehog are 96% identical, even more so in the active signalling portion of the N-terminus.

With respect to claim 44, Applicants submit that one of skill in the art at the time of filing would not only have understood the meaning of 'substantially purified', particularly in light of the definition on page 26, lines 17-31, but would have been able to prepare such a composition.

With respect to claim 51, the Office Action states that the specification "does not enable one of skill to determine what applicants consider about 19 kD ... or how such fragments are of use." Applicants point out that the enablement requirement addresses how to make or use, and that the concerns raised by the Examiner are properly considered as questions of definiteness (35 U.S.C. § 112, second paragraph) and utility (35 U.S.C. § 101). The Examiner's attention is directed to the arguments presented in the portions of this response devoted to those issues.

Furthermore, with respect to claims 40 and 54, although Applicants do not describe an example of using nucleic acids encoding human Ihh or Dhh *in vivo*, the Examiner is reminded that a working example is not required. The specification, from pages 37-40, discusses in considerable detail how to use the claimed nucleic acids *in vivo*, and Applicants contend that this description, taken together with the level of skill in the art at the time of filing, is sufficient to demonstrate enablement of *in vivo* uses of the claimed nucleic acids.

Claims 36 and 72 have been cancelled, rendering the rejection moot with respect to these claims.

Accordingly, Applicants submit that the present claims are enabled throughout their scope, and request reconsideration and withdrawal of this rejection.

5. Claims 49-53 and 72 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended claim 49, and submit that because one of skill in the art would recognize that the term 'N-terminal' would modify a polypeptide, as opposed to a nucleic acid, that any ambiguity with respect to the term 'fragment' is resolved.

Applicants have amended claim 53 to remove the term 'capable of'. Applicants further submit that one of skill in the art would readily understand what features, such as an origin of replication, would be present in a nucleic acid configured for replication in a prokaryotic or eukaryotic cell, and thus the scope of the presently claimed subject matter is definite.

Applicants submit that the use of the term 'about' in claim 51 is not indefinite. As understood by one of skill in the art, the term "about" indicates that the molecular weight of the protein is approximately 19 kD, rather than exactly 19,000 amu. One of skill in the art will recognize that, although the boundary of what is about 19 kD is flexible, the metes and bounds of the term are not unclear. Indeed, as noted in MPEP 2173.05(b), "[t]he fact that claim language ... may not be precise does not automatically render the claim indefinite", and the term 'about' has repeatedly been sanctioned by courts, including the Federal Circuit and the Board of Appeals, in analogous situations.

For example, in *In re Marosi*, 218 U.S.P.Q. 289 (Fed. Cir. 1983), the Federal Circuit found that the applicant had "provided a general guideline and examples sufficient to enable a person of ordinary skill in the art to ... draw the line", and cautioned that "[i]nsofar as it requires appellants to specify a particular number as the cutoff between their invention and the prior art, the PTO's position is impractical." In *Andrew Corp. v. Gabriel Elects., Inc.*, 6 U.S.P.Q.2d 2010 (Fed. Cir. 1988), the Federal Circuit found that one of ordinary skill in the art would know when certain claimed terms are 'substantially equal' or 'closely approximate'; "The criticized words are ubiquitous in patent claims. Such usages, when serving reasonably to describe the claimed subject matter to those of skill in the field of the invention, and to distinguish the claimed subject matter from the prior art, have been accepted in patent examination and upheld by the courts." In *In re Moore*, 439 F.2d at 1235 (Fed. Cir. 1970), the court stated, "This... [indefiniteness]

inquiry... is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity.... [T]he definiteness of the language must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art."

Especially relevant to the pending claims, in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), the Federal Circuit sanctioned a claim directed to "antibodies having an affinity for the antigenic substance of at least *about* 108 liters/mole" (emphasis added), noting that although there may have been "no standard set of experimental conditions which are used to estimate affinities", the claims, read in light of the specification, "reasonably apprise those skilled in the art" and are "as precise as the subject matter permits".

The Examiner has not pointed out why the scope of the term would not be understood, save to point out that one of a number of methods for measuring the weight of a protein can yield variable results. As noted above, the courts have found that neither the availability of a number of methods nor problems of variable results should trigger a finding of indefiniteness, when the claims are as precise as the subject matter permits. Moreover, the Examiner should not require Applicants to specify a particular number as a cut-off where such a limitation is impractical. Accordingly, Applicants submit that the term is clear to one of skill in the art, and respectfully request reconsideration and withdrawal of this rejection.

Claim 72 has been cancelled, thereby rendering this rejection moot.

For the reasons set forth above, Applicants believe that the pending claims, as amended, are sufficiently definite to satisfy 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

6. Claims 35-38 and 44-46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Marigo. Applicants have amended these claims, thereby rendering this rejection moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

7. Claims 35-40 and 42-46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Marigo. Applicants have amended these claims, thereby rendering this rejection moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

8. Claims 38-46, 49-54, 63-70, and 72-74 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillier. Applicants respectfully point out that this reference is not enabling, because it fails to disclose a function or use for the disclosed sequence. Nevertheless, Applicants have amended these claims, and submit that the subject matter of the claims as amended is not anticipated by Hillier. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 832-1000.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our **Deposit Account No. 06-1448.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully submitted,
FOLEY, HOAG, & ELIOT

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